Chapter 11
Genetic Liver Disease

A1a. More fully define the frequency of disease expression associated with *HFE* C282Y and define major modifying factors. In the Hemochromatosis and Iron Overload Screening (HEIRS) Study of approximately 100,000 North Americans, C282Y homozygosity was identified in 0.44 percent of whites but only 0.12 percent of African-Americans and less than 0.1 percent of Asians. Most C282Y homozygotes (88% of men; 59% of women) had high serum ferritin levels; no genetic modifiers have been identified as yet (Adams PC. *N Engl J Med* 2005;352:1769). (20%)

A1b. Identify a cohort of patients with congenital hepatic fibrosis to study its natural history and optimal management. An intramural NIH protocol has been initiated and enrolled 38 patients with autosomal recessive polycystic kidney disease (ARPKD), many of whom have congenital hepatic fibrosis (CHF). Cross-sectional and longitudinal data, genetic testing, and genotype-phenotype studies are underway. (20%)

A2a. Establish DNA evaluation centers of excellence for Wilson disease, the porphyrias, and hemochromatosis. No such centers have been established.(0%)

A2b. Develop a reliable animal model for the liver disease of cystic fibrosis. A mouse model with deletion of the *CFTR* gene has been developed that develops progressive liver disease with steatosis, cholangitis, and inspissated secretions (Durie PR. *Am J Pathol* 2004;164: 1481). This model has potential for evaluation of means of prevention or treatment of the liver disease of CF, as well as analysis of modifier genes for development of liver injury in CF. (20%)

A3. Fully elucidate the molecular mechanisms of intestinal absorption, hepatic metabolism, and biliary excretion of copper. New steps in the pathway of hepatic metabolism of copper have been elucidated, including the role of several transporters and chaperones (Burstein E. *J Biol Chem* 2005;23:2222). (10%)

B1a. Develop and apply practical and accurate screening methods for identifying hemochromatosis before significant tissue injury has occurred. Screening tests for hemochromatosis include transferrin saturation and ferritin. The applicability of these tests in the general population is now being assessed with the HEIRS cohort. (0%)

B1b. Define the role of heterozygosity for Wilson ATPase and *HFE* mutations in other liver diseases. The role of *HFE* mutations in worsening other liver diseases is controversial, particularly in its role in progression of fibrosis in hepatitis C and nonalcoholic steatohepatitis. *HFE* mutations and responses to therapy are currently under investigation. Because of their heterogeneity, the Wilson ATPase mutations have not been analyzed in large cohorts of patients with other liver diseases. (10%)

B2a. Fully define the normal molecular pathways of iron metabolism in humans with specific definition of the roles of HFE and hepcidin. Major advances have been made in the elucidation of the role of hepcidin and other molecules in iron metabolism. Hepcidin acts as a negative regulator of iron absorption by inducing internalization and degradation of the ferroportin transporter in enterocytes and macrophages (Nemeth E. *Science* 2004;306:2090; Donovan. *Cell Metabol* 2005;1:191). The molecular basis for ferroportin-linked hemochromatosis has been further elucidated (De Domenico I. *PNAS* 2005; 102:8955). The divalent metal ion transporter 1 (DMT1, also known as SLC11A2) has been shown to be the major transmembrane iron transporter of the intestine and erythroid precursors, but hepatocytes and other cells have an alterative, as-yet-unknown, iron uptake mechanism (Gunshin H. *J Clin Invest* 2005; 115:1258). (20%)

B2b. Define the role of liver iron levels in the course of NASH, alcoholic liver disease, chronic hepatitis C, and porphyria cutanea tarda. Both serum and hepatic iron levels are often high in patients with chronic liver disease and they often correlate with more advanced fibrosis and poor response to therapy. The pathogenesis of this poor response and possible means of improving responses by iron depletion await further elucidation. (10%)

B3a. Identify the major genetic causes of inherited iron overload among African Americans, Asian Americans, and Hispanics. The classical C282Y *HFE* mutation accounts for few cases of iron overload in African and Asian Americans and Hispanics (Barton JC. *Genetic Testing* 2005; 9:231). Other causes possibly related to mutations in other iron transporters or signaling molecules have yet to be identified. (0%)

B3b. Define the molecular basis of the increase in HCC risk among persons with the porphyrias. Links between the molecular abnormalities of porphyrin metabolism in the inherited porphyrias and pathways of carcinogenesis have not been identified. Iron overload typical of porphyria cutanea tarda and elevated 5-aminolevulinate typical of the acute porphyrias are known to cause oxidative stress, a potential factor in liver carcinogenesis. (0%)

C1. Develop rapid metabolic screening test for Wilson disease that could also be applied to newborns or infants and assess test for efficacy and risk-benefit ratio. Until there is a more complete understanding of copper metabolism and its control, there is unlikely to be a rapid metabolic screening test for Wilson disease. Testing for the most common Wilson ATPase mutations might identify 30 to 40 percent of cases, but this approach is currently not practical for screening purposes. (0%)

C2a. Define specific genetic modifiers of Wilson disease and porphyrias using animal models and clinical cohorts of patients. In large patient cohorts from Europe and the United States, no genetic modifiers of Wilson disease have been identified. (0%)

C2b. Develop an improved therapy for amelioration of acute crises in porphyria. Intravenous hemin therapy remains the recommended therapy of severe acute crises (Anderson K. *Ann Intern Med* 2005;142:439), but a possible new approach using recombinant porphobilinogen deaminase is now in phase I/II clinical trials. (0%)

C3a. Develop noninvasive means of accurately defining total body and hepatic iron and copper, either using imaging studies or mathematical models and serum levels of related molecules. MR techniques are capable of measuring iron levels associated with severe iron overload and are being refined to provide more accurate and sensitive quantitative assessments (St Pierre TG. *Ann NY Acad Sci* 2005; 1054:379). Special MRI algorithms have been approved for clinical use in the United States. (20%)

C3b. Develop practical gene or stem cell therapy for AIP and EPP. No gene therapies for AIP or EPP have been developed, although liver transplantation may be effective for intractable cases. Gene therapy research is promoted by NIH-funded Molecular Therapy Centers. (0%)

Figure 13. Estimated Progress on Genetic Liver Disease Research Goals, 2005 (Year 1)